REMARKS

I. CLAIM STATUS AND AMENDMENTS

Claims 1-39 were pending in this application when last examiner.

Claims 1-39 were examined on the merits and rejected.

Claims 14 and 18 are amended to delete "a hydrogen atom, a substituted or unsubstituted straight chain or branched chain C_{1-6} alkyl group or C_{1-6} alkoxy group, a substituted or unsubstituted C_{3-8} cycloalkyl group or a C_{3-8} cycloalkoxy group, or an aralkyl group" from the definitions of R^1 and R^2. Claims 14 and 18 are further amended to introduce the limitations of claims 15 and/or 16. Finally, claim 18 is amended to include a limitation of claim 14.

Claim 15, 16 and 22 are cancelled without prejudice or disclaimer thereto. Applicants reserve the right to file a divisional or continuation application on any cancelled subject matter.

Claim 17 is amended to conform to the other claim amendments.

Claim 24 is amended to clarify the claimed invention.

No new matter has been added.

II. OBJECTION TO THE SPECIFICATION AND CLAIMS

On page 2 of the Office Action, the specification was objected to for not containing a "Brief Description of the Drawings" heading. The specification is amended to correct this informality and therefore this objection is moot.

On page 2, claims 9-11 and 26-28 were objected to for failing to further limit the subject matter of the claims upon which they depend. Applicants respectfully traverse these objections, as applied to the amended claims.

In regards to the objection to claims 9 and 26, Applicants note that these claims further require a "pharmaceutically acceptable carrier" and therefore further limit the claims they refer to.

In regards to claims 10-11 and 27-28, Applicants note such claims are method claims and require an active step such as mixing or administering. Therefore, such claims also further limit the claims they refer to.

Also on page 2, claim 19 was objected to for failing to further limit the subject matter of the claim upon which it depends. In particular, the Office contended that this claim was broader than claim 18, from which it depends. Claim 18 is amended to optionally include all the components of claim 19.

Thus, for the above noted reasons, these objections are moot and should be withdrawn.

III. ENABLEMENT REJECTION

On pages 3-5, claims 1-11 and 29-36 were rejected under 35 USC § 112, first paragraph, because the specification, while being enabling for the compounds of formula (I), their pharmaceutical compositions and methods of using such compounds in the treatment of psychotic conditions, does not reasonably provide enablement for pharmaceutical agents having serotonin 5-HT_7 receptor antagonist activity and muscarinic M_4 receptor agonist activity for use in treating psychotic conditions where the agent does not include a particular set of bisarylazepine compounds.

Applicants respectfully traverse this rejection.

The Office contends that the specification does not provide enablement for those members of the group of combined M_4 agonists/5-HT_7 antagonists that are not specifically described in the specification. Applicants contend that the claims are not overly broad, and that the amount of additional experimentation required to put the invention into practice, for this additional group of compounds, is relatively minor in relation to the magnitude of the invention described in the specification.

In relation to the specific factors under consideration:

a) Breadth of claims – the claims are not in fact as broad as they might initially appear. From the complete set of compounds that have been characterized pharmacologically, only a handful exhibit both 5-HT_7 antagonist activity and M_4 agonist activity. Hence this is not a common property of compounds. It is likely that the universe of compounds with 5-HT_7 antagonist activity will represent a large number of compounds. However, it is likely that the number of compounds in the universe of compounds with M_4 agonist

activity is rather small, since only a minor proportion of agents active on G-protein-coupled receptors are able to induce conformational changes sufficient to induce signaling responses (i.e. act as agonists). The number of compounds in the intersection of these two groups – the universe of compounds with both M_4 agonist activity and 5-HT_7 antagonist activity - is in fact likely to be relatively small. It should also be noted that the scope of the claim is readily discernible, as the skilled person can easily determine whether a particular compound meets the requirements of the claim, by being able to determine if the compound possesses antagonistic activity against the serotonin 5-HT_7 receptor and agonist activity against the muscarinic M_4 receptor. Thus, the specificity of this claim is clear.

b), c) Nature of invention and state of prior art – As noted in the specification (pp. 1-3) all existing drugs used to treat schizophrenia are only effective against some of the symptoms and give rise to unpleasant side-effects – leading to the poor prognosis and life-long debility and suffering for the majority of patients with the disease. All groups involved in the care and treatment of patients with schizophrenia, without exception, acknowledge the urgent need for more effective and less unpleasant treatments for the disease. Thus, while the prior art does teach compounds that can be used to treat some aspects of schizophrenia, it does not teach compounds that can be used to treat schizophrenia fully, effectively and without causing distress. The existing drug with the best overall efficacy, albeit compromised by a particularly bad side-effect profile – is clozapine. Decades of research have attempted to decipher the mechanisms underlying the improved efficacy of clozapine relative to similar drugs. However, clozapine has affinity for a very large number of receptors. This broad, non-selective pharmacology has contributed to the difficulty in identifying the pharmacological mechanisms underlying clozapine's superior therapeutic efficacy as compared to other antipsychotic drugs. The present application thus represents an extremely important realization, in identifying that combined activity at M_4 and 5-HT_7 receptors yields an extremely efficacious strategy for treating schizophrenia. The specification teaches for the first time how clozapine exerts its superior therapeutic profile, and also how to produce an anti-psychotic drug superior to clozapine. Thus considering the nature of the invention and the

condition of the prior art, the amount of further experimentation required to put the invention into use is relatively minor.

d) Level of skill in the art – Applicants note that the information disclosed in the specification is sufficient to enable those skilled in the art to practice the claimed invention without undue experimentation.

e) Level of predictability in the art – The specification describes two distinct but equally effective routes to obtaining antagonistic activity against the serotonin 5-HT_7 receptor and agonist activity against the muscarinic M_4 receptor – the provision of working examples is thus strong, increasing predictability. In addition, it is well-known that predictability, in the discovery of novel drugs to improve the treatment schizophrenia, has been extremely low for many decades. This is evident not only from the experience of all those working in this area, but also from the minimal advances in the treatment of the disease. This low predictability derives largely from a lack of knowledge as to where pharmacologically to target novel drug candidates. Only a minor component of the low predictability is due to difficulty in deriving an appropriate compound through medicinal chemistry, once the target is decided, as this can almost invariably be achieved with sufficient resources. This is clear from the large number of compounds successfully synthesized to act at various receptor targets, without any clear advances in the treatment of the disease over the last few decades. Therefore, the invention described in this specification dramatically increases the predictability for the discovery of new and improved antipsychotic drugs, and the predictability of additional experimentation required to practice the invention (and produce an improved anti-psychotic drug) is high, relative to equivalent studies not taught by this specification.

f),g), Amount of direction and guidance provided by the inventor – The specification teaches very clearly how to obtain a drug to treat the positive and negative symptoms of schizophrenia, and thus to be superior to all existing antipsychotic drugs. The specification describes not only the use of prototypical compounds – an M_4 agonist (PTAC) and a 5-HT_7 antagonist (SB257841) whose basic receptor pharmacological

profiles are extremely well-known in the art – but also novel compounds identified on the basis of the specified dual M_4/5-HT_7 action. Thus, an extremely convincing and unambiguous set of working examples are provided in the specification. The amount of direction, with these two different classes of compounds, is substantial. The demonstration of the activity in two different classes/combinations of compounds dramatically increases predictability and teaches directly how to make and use the invention.

h) Level of experimentation needed to use the invention - The Office contends that only way to determine the metes and bounds of the instant claims would be to synthesize the infinite set of compounds which are not excluded by the claims and assay them for the claimed activities. However, it is not the case that only some of these compounds will have antipsychotic activity, and therefore further experimentation is required. Sufficient evidence is provided in the specification, without the need for any additional experimentation, that the full scope of compounds claimed will operate as anti-psychotic drugs. As noted above, we not only use prototypical compounds – an M_4 agonist (PTAC) and a 5-HT_7 antagonist (SB257841) whose basic receptor pharmacological profiles are extremely well-known in the art – but also use novel compounds identified on the basis of the specified dual M_4/5-HT_7 action. Therefore, the claims are certainly supported by enabling disclosures, with the data from the prototype selective compounds and also the synthesized example compounds providing an overwhelming case that the compounds claimed can be used for the described therapeutic action. Applicants therefore note that the amount of experimentation is not undue, considering the relationship of the invention to the prior art."

Therefore, for the above noted reasons, this enablement rejection is untenable and should be withdrawn.

IV. INDEFINTENESS REJECTION

On pages 5-6, claims 12-28 and 37-39 were rejected under 35 USC § 112, second paragraph, as indefinite. Applicants respectfully traverse this rejection, as applied to the amended claims.

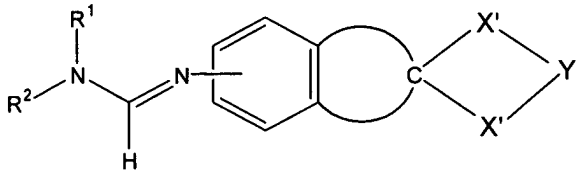
In particular, claims 12-13 were rejected for the term "test procedure(s)". Applicants note that test procedures included the use of radioligand binding techniques to assess the binding affinity of a compound for the specified receptor. These techniques are well-known to those skilled in the art. They involve the measurement of the amount of a radioactively-labeled ligand, specific for the receptor, which is bound to cell membranes containing the receptor, in the presence of increasing concentrations of test compound.

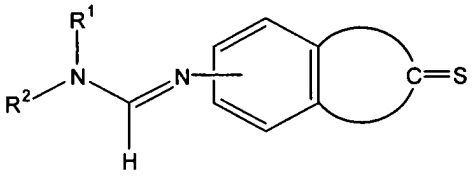
Also, Applicants further note that test procedures include the use of signaling assay techniques to assess the efficacy of a compound for a specified receptor. These techniques are well-known to those skilled in the art. They typically involve the measurement of the amount of G-protein activation subsequent to binding of the compound to the receptor, in cell membranes containing the receptor, using a radioactive GTP analogue. Alternatively, they can involve the measurement of signaling molecules produced in the cell subsequent to receptor activation, for example using a cAMP ELISA or enzyme-immunoassay.

Examples of these techniques are provided in the specification (refer to specification, Example 2, page 38, line 26 to page 39, line 18 and page 40, line 5 to page 41, line 3).

Therefore, this rejection as applied to claims 12-13 is untenable and should be withdrawn.

Further, claim 14 was rejected as indefinite for the noted phrase. Applicants respectfully disagree and request the Examiner to reconsider this rejection. For clarity, the Applicants note that Compound 28, and the deprotected form thereof, on page 28 of the specification are embodiments of the rejected phrase. These are shown below:





Therefore, Applicants respectfully suggest this rejection is untenable and should be withdrawn.

Finally, Claim 24 was rejected as indefinite for the term "substantially." This phrase has been deleted and therefore this rejection is moot.

V. ANTICIPATION REJECTION

On page 6, claims 14 and 18 were rejected under 35 USC § 102(b) as anticipated by DE 2849558 (CAPLUS abstract). Further, claims 14, 18 and 22 were rejected under 35 USC § 102(b) as anticipated by Chemical Abstracts Service XP002287521.

These rejections, as applied to the amended claims, are respectfully traversed.

For the convenience of the Examiner, attached hereto are diagrams of the compounds described in the cited documents "DE2849558" and XP002287521". Applicants note that the substituents corresponding to R_1 or R_2 in the compounds in the cited art are hydrogen, methyl or substituted phenyl.

Applicants further note that the claimed subject matter has been limited to the embodiment where R_1 or R_2 are bonded to form a cyclic amine, and no longer encompasses the cited compounds. Therefore, this rejection is moot.

CONCLUSION

In view of the foregoing amendments and remarks, the present application is in condition for allowance and early notice to that effect is hereby requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,

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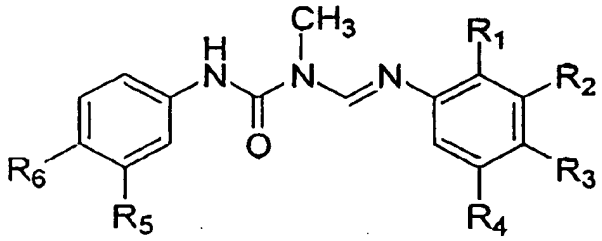
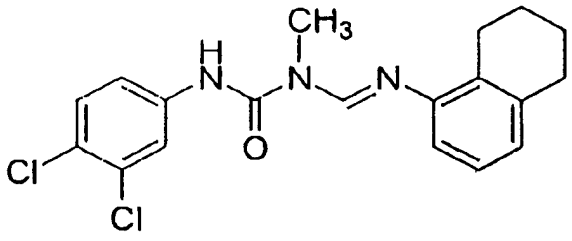
Attachments

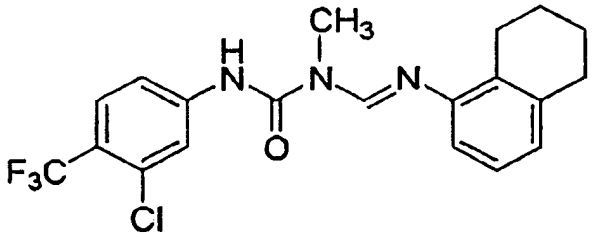
Attachment 1: Diagrams of the compounds described in the cited documents DE2849558 and XP 002287521.

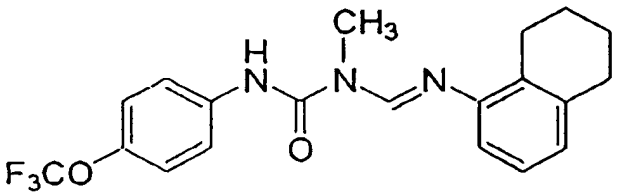
Attachment 1

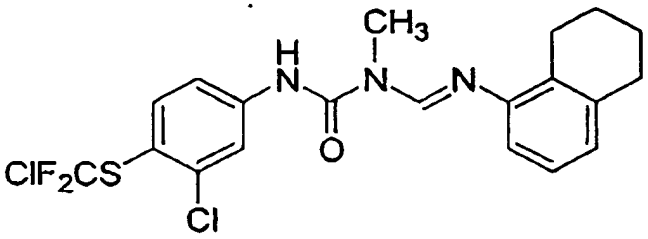
DE2849558

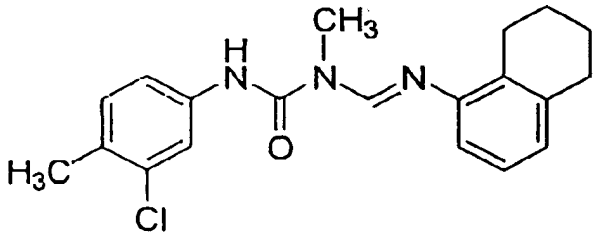


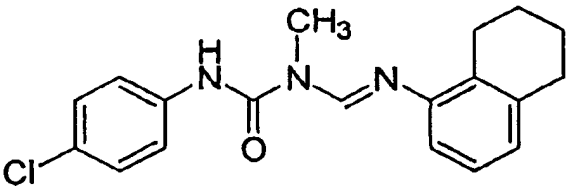


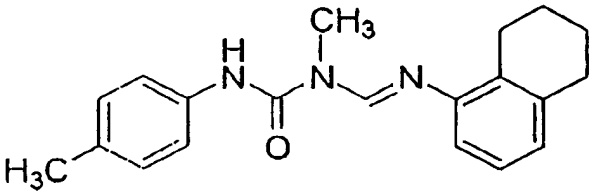


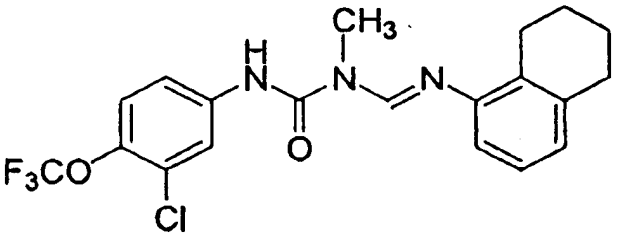


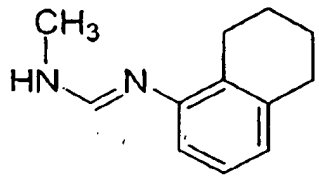












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